REMARKS

Claims 1-3, 7-15, 20-24 and 28 are pending. Claim 30 has been canceled. Claims 4-6, 8-12, 15-18 and 25-27 have been withdrawn.

Applicants wish to thank Examiner Wang for the courtesies extended to their representative, David L. Kershner (Reg. No. 53,112), during a telephonic interview on July 21, 2004.

I. THE REJECTION OF CLAIMS 1-3, 7, 13, 14, 20-24, 28 AND 30 UNDER 35 U.S.C. § 103(a)

Claims 1-3, 7, 13, 14, 20-24 and 28 (claim 30 having been canceled) stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over United States Patent No. 5,998,457 to Kaddurah-Daouk ("Kaddurah-Daouk") in view of United States Patent No. 4,772,591 to Meisner ("Meisner"), United States Patent No. 5,888,553 to Grant *et al.* ("Grant"), United States Patent No. 5,756,496 to Beale *et al.* ("Beale '496") and United States Patent No. 5,716,926 to Beale *et al.* ("Beale '926") set forth in the Office Action. Applicant respectfully disagree.

A. CLAIMS 1-3, 7, 13, 14 AND 20-22 ARE NOT OBVIOUS OVER KADDURAH-DAOUK IN VIEW OF GRANT, MEISNER, BEALE '496 AND BEALE '926

Claims 1-3, 7, 13, 14 and 20-21 are directed to a method of treating a bone or cartilage condition comprising administering to an animal a therapeutically effective amount of an agent comprising creatine, or an analogue or pharmaceutically acceptable salt thereof, to treat bone or cartilage conditions; and claim 22 is directed to a method of promoting growth and mineralization of bone or cartilage cells and tissues comprising administering to a subject a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof. Claims 1-3, 7, 13, 14 and 20-22 further specify that the agent comprising creatine "is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine."

During the interview of July 21, 2004, Examiner Wang acknowledged that none of the cited references disclosed, taught or suggested using creatine that is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine. However, Examiner Wang took the position that the use of such creatine would have been obvious to one of skill in the art in view of the references. Applicants respectfully disagree.

As stated in the present application, "[i]t has been found that dihydrotriazine is a toxic impurity of commercially available creatine and that it has an adverse effect for the patient" (specification, page 29, lines 33-35) (emphases added). The specification further states that "the agent should be essentially free of dicyano-diamide, which is also a toxic impurity of commercially available creatine" (specification, page 30, lines 1-2) (emphases added). The present application still further states that "the agent is essentially free of creatine as a natural degradation product of creatine" (specification, page 30, lines 3-4). Thus, as stated in the present application, commercially available creatine contains dihydrotriazine, dicyano-diamide, or creatinine impurities which can have an adverse effect on the patient. In contrast, Kaddurah-Doak states (Kaddurah-Doak, col. 4, lines 64-67): "Both creatine and creatine phosphate (phosphocreatine) can be extracted from animals or tissue or synthesized chemically. Both are commercially available" (emphasis added). Thus, Kaddurah-Doauk does not disclose, teach or suggest using creatine that is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine. The other references cited in the Office Action (Grant, Meisner and Beale '496) are silent as to the source, grade or required purity of creatine and do not disclose teach or suggest creatine that is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine. In addition, Beale '926 does not even disclose or suggest using creatine. Thus, none of the references cited in the Office Action, either alone or in combination, disclose, teach or suggest using creatine that "is essentially free of one or more of dihydrotriazine, dicyano-diamide, or creatinine."

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). It is never appropriate to rely solely on "basic knowledge" or "common sense" to one of ordinary skill in the art without evidentiary support in the record upon which a rejection was based. *In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001).

As reasoned above, the combination of Kaddurah-Daouk, Grant, Meisner, Beale '496 and Beale '926 does not disclose, teach or suggest a method of using an agent comprising creatine that is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine, which impurities are found in commercial creatine. In addition, there is no evidence in the record to support an assertion of that use of such creatine would be common knowledge to one of ordinary skill in the art as required by *Zurko*. Therefore,

claims 1-3, 7, 13, 14 and 20-22 which recites creatine that is "is essentially free of one or more of dihydrotriazine, dicyano-diamide, or creatinine" are not *prima facie* obvious over Kaddurah-Daouk, Grant, Meisner, Beale '496 and Beale '926.

In view of the above, Applicants respectfully request that the rejection of claims 1-3, 7, 13, 14 and 20-22 under 35 U.S.C. § 103(a) as being allegedly obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926 be withdrawn.

B. CLAIMS 22-24 AND 28 ARE NOT OBVIOUS OVER KADDURAH-DAOUK IN VIEW OF GRANT, MEISNER, BEALE '496 AND BEALE '926

The Office Action alleges that claims 22-24 and 28 (claim 30 having been canceled) are obvious over Kaddurah-Daouk in view of Meisner, Grant, Beale '496 and Beale '926 for the reasons stated in the Office Action. During the interview of July 21, 2004, Examiner Wang stated that the cited references generally taught the use of creatine to treat a bone disorder, and posited that the methods recited in claims 23, 24 and 28 were obvious over the cited references. Applicants respectfully disagree.

First, as discussed above, the combination of Kaddurah-Daouk, Grant, Meisner, Beale '496 and Beale '926 does not disclose, teach or suggest a method of using an agent comprising creatine that is essentially free of one or more of dihydrotriazine as specified in claim 22. Therefore, claim 22 is not obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '496 and Beale '926 for at least this reason.

Kaddurah-Daouk is directed to "a method of treating or preventing a metabolic disorder which relates to an imbalance in the regulation of body weight" (Kaddurah-Daouk, col. 2, lines 44-46). Kaddurah-Daouk states that these include "obesity and its related disorders (such as cardiovascular disease, hypertension, diabetes, hyperlipidaemia, osteoporosis and osteoarthritis) and severe weight loss" (Kaddurah-Daouk, col. 2, lines 46-49). However, as conceded in the Office Action, "Kaddurah-Daouk does not expressly teach the employment of creatine pyruvate for the treatment, or the particular amount administered, or the method may be employed for promoting growth and mineralization of bone, improving acceptance and osseous integration of bone, or accelerating healing as claimed in claims 22-24" (Office Action, page 2, ¶ 4). These deficiencies of Kaddurah-Daouk are not overcome further in view of Grant, Beale '496, Beale '926 and Meisner.

Grant is directed to the use of chromium to regulate enzyme functions and decrease serum cortisol (Grant, column 3, lines 25-26). The Office Action states that "Grant et al. teaches that the excess cortisol is known to be a cause of osteoporosis, tissue degeneration, and an anabolic composition with anticortisol effect are [sic] used to balance effect of cortisol. The anabolic composition comprising creatine" (Office Action, page 2, ¶ 5). Applicants agree that Grant teaches the catabolic effect of cortisol. However, Applicants submit that Grant does not teach or suggest the use of creatine to regulate cortisol. For example, Grant expressly teaches: "These and other objects may be accomplished by a composition...comprising effective amounts of a chromium salt, complex or chelate and a magnesium glycyl glutaminate and, optionally, one or more additional nutrients selected from the group consisting of a magnesium amino acid chelate or proteinate, an α-glutaric acid salt of ornithine, creatine or a salt thereof, and a branched chain amino acid selected from the group consisting of leucine, isoleucine and valine and mixtures thereof" (Grant, column 5, lines 56-62) (emphasis added). Grant provides no teaching or suggestion to select "creatine, or a salt thereof" from the recited list of "optional" additional nutrients, or even that creatine is useful for regulating cortisol levels as taught by Kaddurah-Daouk. Furthermore, Grant provides no teaching or suggestion to use creatine in a method to treat a bone or cartilage disorder, let alone a method for improving osseous integration of bone implants, accelerating the healing in a subject having a defect in bone or cartilage, or treating osteoarthritis unrelated to weight gain or weight loss.

The Office Action acknowledges the limitations of Grant but states "[t]he lack of express teaching by Grant that creatine is cortisol antagonist would not week [sic] the over all rejections since Beale disclosed that creatine pyruvate, the elected creatine compound, is a cortisol antagonist" (Office Action, page 5, ¶ 6). For the reasons discussed above, Applicants submit that Grant not only lacks an "express teaching ... that cortisol is a cortisol antagonist," but Grant's express teachings to use chromium as a cortisol antagonist would teach away from using creatine. These deficiencies of Kaddurah-Daouk and Grant are not remedied further in view of Beale '469 and Beale '926.

Beale '469 is directed "to a composition which comprises pyruvate and/or derivatives of pyruvate and an anti-cortisol or cortisol blocker compound" (Beale '469 , col. 2, lines 11-13). The Office Action alleges that "Beale ('469) teaches creatine pyruvate (pyruvyl-creatine) is particularly useful as cortisol antagonist or cortisol blocker for prevent [sic] the catabolic activity of cortisol" (Office Action, page 3, lines 4-6). However,

Applicants submit that Beale '469 expressly teaches that "[c]reatine monohydrate is an additional cortisol blocker that, when combined with pyruvate, produces a synergistic effect in increasing the lean body mass of a mammal" (Beale '469, col. 3, lines 58-60) (emphasis added). Beale '469 is silent as the use of creatine to treat a bone disorder. Thus, even if Beale '496 in combination with Kaddurah-Daouk and Grant teaches the use of creatine pyruvate to treat obesity or increase lean body mass, that combination of references does not teach or suggest a method for using creatine, pyruvate, or creatine combined with pyruvate to treat a bone or cartilage disorder, let alone a method for improving osseous integration of bone implants, accelerating the healing in a subject having a defect in bone or cartilage, or treating osteoarthritis unrelated to weight gain or weight loss.

Beale '926 is directed to the use of "pyruvate in combination with an anabolic protein composition" (Beale '926, Abstract) and describes "the treatment of osteoporosis by the administration of calcium pyruvate" (Beale '926, col. 5, lines 16-17). The Office Action alleges that "Beale ('926) further teaches that pyruvate is known to be useful for treating osteoporosis" (Office Action, page 3, lines 8-9). However, Beale '926 does not even disclose, teach or suggest creatine. Thus, the combination of Beale '926 with Kaddurah-Doak, Grant and Beale '496 does not teach or suggest a method of using creatine to treat a bone or cartilage disorder, let alone a method for improving osseous integration of bone implants, accelerating the healing in a subject having a defect in bone or cartilage, or treating osteoarthritis unrelated to weight gain or weight loss.

With respect to Meisner, the Office Action alleges that "Meisner teaches a method for accelerated wound healing or treating degenerative disorders including periodontal disease, [or] osteoarthritis, comprising administering a composition comprising creatine to an animal or human" (Office Action, page 3, lines 1-4). However, Applicants submit that Meisner is directed to a method which "comprises the administration of four substances: a source of biologically available calcium; ascorbic acid; a precursor or stimulant of epinephrine or nor-epinephrine production selected from tyrosine and phenylalanine; and a mild anti-inflammatory substance selected from the anti-inflammatory members of the group consisting of simple sugars, amino sugars, amino acids, and derivatives thereof" (Meisner, col. 2, line 67 - col. 3, line 6). Meisner is silent as to the use of creatine for treating obesity as taught by Kaddurah-Doak, for increasing lean muscle mass as taught by Beale '496, or as a nutrient as taught by Grant. Therefore, one of skill in the art would find no suggestion to combine Meisner with Kaddurah-Doauk and Beale '496 for at least this reason. Moreover, Meisner describes a number of mild anti-inflammatory substances, one being creatine

(Meisner, col. 5, lines 10-19). However, Meisner does not exemplify creatine nor does Meisner teach or suggest that creatine is preferred to any of the other anti-inflammatory substances. Rather, Meisner expressly teaches that "cysteine is preferred because it is bactericidal against Streptococcus mutans in addition to being anti-inflammatory in action" (Meisner, col. 4, lines 56-58) (emphasis added). Therefore, the combination of Beale '926 with Kaddurah-Doak, Grant and Beale '496 does not teach or suggest a method of using creatine to treat a bone or cartilage disorder, let alone a method for improving osseous integration of bone implants, accelerating the healing in a subject having a defect in bone or cartilage, or treating osteoarthritis unrelated to weight gain or weight loss.

In summary, even if Kaddurah-Daouk further in view of Grant, Beale '496, Beale '926 and Meisner teaches a method of controlling obesity or lean muscle mass by regulating cortisol levels, the combination of references does not teach or suggest that creatine should be used in a method to treat a bone disorder, let alone a method to improve acceptance and osseous integration of bone implants, accelerate the healing in a subject having a defect in bone or cartilage, or treat osteoarthritis unrelated to weight gain or weight loss.

To make out a prima facie case of obviousness the references cited to reject the claims must provide all of the elements of the invention as claimed and a suggestion must be found within the references themselves to combine the disclosures of the various cited art references to make the claimed invention. *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Graylock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery*, 804 F.2d 135, 140 (Fed. Cir. 1986); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984).

For the reasons discussed above, Kaddurah-Daouk further in view of Grant, Beale '496, Beale '926 and Meisner does not disclose, teach or suggest that creatine, a creatine compound, or an analog thereof, should be used in a method to improve acceptance and osseous integration of bone implants, accelerate the healing in a subject having a defect in bone or cartilage, or treat osteoarthritis unrelated to weight gain or weight loss. In particular, Grant (teaching the use of chromium to regulate cortisol) and Meisner (teaching that cysteine is preferred) would lead away from the use of creatine according to *W.L. Gore*

& Associates, while Beale '469 (silent as to the use of creatine to treat a bone or cartilage disorder) and Beale '926 (silent as to the use of creatine) would not provide any suggestion to use creatine to treat a bone or cartilage disorder. Therefore, one of skill in the art would find no motivation to modify the teachings of Kaddurah-Daouk further in view of Grant, Beale '469, Beale '926 and Meisner, and use creatine, a creatine compound, or an analog thereof, in a method to improve acceptance and osseous integration of bone implants as recited in claim 23, accelerate the healing in a subject having a defect in bone or cartilage as recited in claim 24, or treat osteoarthritis unrelated to weight gain or weight loss as recited in claim 28. Therefore, claims 23, 24 and 28 are not *prima facie* obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '496 and Beale.

In view of the above, Applicants respectfully request that the rejection of claims 22-24 and 28 under 35 U.S.C. § 103(a) as being allegedly obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926 be withdrawn.

II. CONCLUSION

Applicants respectfully submit that the present claims are now in condition for allowance and request an early issuance of a Notice of Allowance in connection with the present application. No fee is believed to be due. In the event an additional fee is required, please charge the required fee to Jones Day Deposit Account No. 50-3013.

If the Examiner wishes to discuss this case, then Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and expedite the allowance of the application.

Respectfully submitted,

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